REMARKS

Upon entry of the amendment, claims 27-57 will be pending in the application. Claims 1-26 have been cancelled as drawn to non-elected subject matter. Claims 27, 30-35, 38-44, 47, 50-52, and 54 have been amended. New claims 56 and 57 have been added. Support for the term "fractionated" and "fractionating" in amended claim 27 is supported at least on page 22, line 2-page 23, line 18 of the specification. Recitation of the "recovered" subset is supported at least in claim 27 as originally filed. Amending the original designations of "first subset " and "second subset" to recite "set" and "subset", respectively, is intended more particularly to point out and distinctly claim the invention without substantively affecting the scope or breadth of the recited subject matter. These amendments draw their support from the claims as originally filed.

The amendments to claim 30 are supported in claim 30 as originally filed, and are made in order more particularly to point out and distinctly claim the invention, in part to avoid ambiguity with the first library recited in claim 27. The amendments to claims 38-42 inserting the recitation "from one another" is supported on page 8, lines 11-12, on page 22, line 7, and in Fig. 11 Panels A-D, and especially in Panels C and D. In Figure 11, the numbers to the right of the MP gel images in each panel refer to the length in nucleotides of the standard nucleic acids repeating in alternate lanes and demonstrate the ability to resolve nucleic acids having different sizes as enumerated in number of nucleotides. The amendments to claim 50 such that it now recites "member nucleic acid molecules" is supported generally by the claims as originally filed as well as on pages 23-45 of the specification, and is made in order to provide unambiguous antecedent basis in claim 27 for the recited phrase. The further amendment to claim 50 reciting "pooling" is supported on page 23, and in Figures 7 and 9, of the specification. Additional

amendments to the claims likewise are made to correct various informalities (such as antecedent bases for the various recitations, and to correct minor grammatical errors).

Support for new claims 56 and 57 is found on pages 23-45 and in Figures 7 and 9 of the specification. No new matter has been added. An Appendix showing amendments to the claims follows the Response.

Cancellation of claims or amendment of claims does not represent a concession by Applicants that the subject matter no-longer claimed is not patentable. Applicants reserve the right to pursue the subject matter of cancelled claims in subsequent applications.

Claims 27-55 were examined in the Office Action. The examined claims are rejected as obvious, on various grounds.

Claim Objections

Claim 44 was objected to for misspelling "endonuclease". The claim has been amended to correctly spell this term.

Rejection under 35 USC 112, second paragraph

Claims 38-42 are rejected as indefinite for reciting the phrase "the first subset of nucleic acids differ by...." Claims 38-42 have been amended to recite that members of the set of nucleic acid molecules differ from one another by specified numbers of nucleotides in length. This recitation addresses the concern expressed in the Office Action that the comparison for the difference was not specified. The Office Action also queried whether the difference was in length, base, etc. Applicants respectfully note that claims 38-42 as originally filed recite "nucleotides in length", and that this phrasing addresses the concern raised by the Office Action.

Claim 50 was rejected as indefinite for reciting the phrase "two or more members of the library are combined prior to separating the second subset." Claim 50 has been amended to recite "member nucleic acid molecules". This recitation provides an unambiguous reference as antecedent to the identical recitation in amended claim 27, step (d). This antecedent particularly points out the origin of the nucleic acid molecules as members of the subset. Claim 50 has further been amended such that it now recites "pooling". This term appears in the description of multiplex sizing appearing on pages 23-45 of the specification, and serves to overcome the concern expressed in the Office Action concerning the use of the term "combined". These amendments are believed to overcome the rejection.

Claims 27-55 were rejected as indefinite for reciting the phrase "a first subset of nucleic acid molecules further comprising at least a second subset of nucleic acid molecules . ." Claim 27, and claims depending from claim 27, have been amended by replacing the original designations of "first subset " and "second subset" to recite "set" and "subset", respectively, in order more particularly to point out and distinctly claim the invention without substantively affecting the scope or breadth of the recited subject matter. In addition, claims 27 and claims depending therefrom have been amended so that terms "fractionated" and "fractionating", "recovered", and "isolated" are used with the intent of more particularly pointing out and distinctly claiming the stepwise flow of the method of the invention. These amendments are believe to overcome the rejection of claims 27-55.

In summary, Applicants have amended claims 27-55 in order to overcome the various rejections of these claims under 35 U.S.C. §112, second paragraph. Reconsideration and withdrawal of the rejection is requested.

Rejection under 35 USC 103 (a)

Claims 27-42 and 47-55 are rejected as prima facie obvious over Kamb et al., U.S. Patent No. 6.020,240 ("Kamb") and Okayama, Mol. Cel. Biol. 2:161-70 ("Okayama"). The rejection is traversed as applied to the claims as amended.

In performing analysis for determining whether a claimed invention is prima facie obvious over the prior art (See MPEP § 2141 Rev. 1, Feb. 2000):

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; [and]

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention;

citing Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Applicants note that the invention now claimed recites a method that includes two fractionation steps: one fractionation step carried out on the population of nucleic acid molecules to provide the set of nucleic acid molecules (step (b)), and an additional fractionation step carried out on the recovered nucleic acids to provide the recovered subset (step (f)).

The combination of Kamb and Okayama, when considered as a whole (as specified in MPEP 2141, above), fails to suggest the desirability of the claimed invention. Applicants note initially that there are several deficiencies in relying on Kamb as a reference. First, Kamb, in the section referenced in the Office Action, does not teach two fractionation steps such as required in either claim 27 or new claim 56. More specifically, Kamb does not teach "providing a population of nucleic acid molecules...[and] separating and isolating the first subset [now recited as a set]..." as well as "recovering nucleic acids...and isolating a nucleic acid molecule..." (emphasis added). At most, Kamb discloses only a single step that separates nucleic acids from

one another, namely, the preparation of gene libraries in vectors or plasmids that are propagated in cells, and screening them according to procedures such as biochemical screens or genetic screens (col. 26, line 49-col. 27, line 21). By not disclosing two fractionation steps Kamb does not provide elements of the presently claimed method of identifying a nucleic acid. Therefore the assertion in the Office Action that Kamb provides both a separating step and an isolating and recovering step (page 7, top) is incorrect. Accordingly, Kamb cannot be properly used as part of the obviousness rejection.

Additionally, the Office Action states "...and isolating a nucleic acid molecule from the second subset [now "set"] (this could be accomplished by simply excising any part of the first subset, or amplifying a part of the first subset [now "subset"])". [Emphasis added] (page 7, first paragraph). As indicated by the use of the word "could", this statement is a surmise added by the Examiner and is not directly attributable to Kamb. Therefore the surmised statement may not properly be cited against the present invention in support of a case of obviousness.

Further, Kamb, when considered as a whole, addresses a different problem from that of the present invention, which is identifying a nucleic acid sequence. Specifically, Kamb relates to a method for the comparative assessment of the level of specific nucleic acid sequences in samples derived from different sources (see Abstract and col. 5, lines 55-62). According to tenet (B) articulated in MPEP 2141, the Examiner may not consider a portion, such as columns 26-27 (see Office Action, pages 5-7), without relating the disclosure to the reference as a whole. Applicants submit that an art worker seeking to identify a nucleic acid sequence would not have turned to a reference, such as Kamb , that addresses a different problem, namely that of the comparative assessment of the level of specific nucleic acid sequences in samples derived from different sources.

Furthermore, according to MPEP 2141, the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. By isolating the disclosure of cols. 26-27 of Kamb, the Office Action appears to have engaged precisely in just such impermissible hindsight.

In summary, Kamb fails as a reference against the present invention because a) it does not disclose two fractionation steps, b) an artisan would not have turned to Kamb in order to solve the problem of identifying a nucleic acid sequence, and c) applying Kamb represents impermissible hindsight reconstruction.

The deficiencies of Kamb are not overcome by Okayama. Okayama similarly does not disclose a method comprising the sequence of steps recited in claim 27 and which includes two fractionation steps.

Finally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (MPEP Section 2143). The Office Action cites Okayama on page 7, 2nd paragraph, without offering any basis for modifying Kamb, or for combining their teachings. Therefore the prima facie case of obviousness based on Kamb in view of Okayama fails.

Additional limitations presented in the claims depending from claims 27 and 56 further render the claimed invention non-obvious in view of the cited references. Applicants note that claims specifying length differences (claims 38-42), pooling (claim 50), a replaceable matrix formulation (claim 53) and multiplexing (claim 57) are not disclosed or suggested in any way in the cited references. These dependent claims are therefore clearly not obvious over the cited Kamb and Okayama.

In view of the foregoing comments, reconsideration and withdrawal is requested of the rejection for obviousness over the combination of Kamb and Okayama.

Claims 43-46 are rejected as obvious over the combination of Kamb, Okayama, and further in view of Macevicz et al., US Patent No. 6,136,537 ("Macevicz"). The rejection is traversed to the extent it is applied to the claims as amended.

Claims 43-46 depend from claim 27. Applicants have demonstrated above that claim 27 is nonobvious over Kamb in view of Okayama. Macevicz fails to supply what is lacking in Kamb and Okayama. Therefore not all the features of claims 43-46, including those recited in the base claim, claim 27, are found in the cited references. Claims 43-46 are therefore nonobvious over the combination of Kamb, Okayama, and Macevicz.

In addition, Macevicz, considered as a whole, addresses a different problem from that of identifying a nucleic acid sequence. Specifically, Macevicz relates to a method for analyzing the frequency of sequences in a population of polynucleotides. Restriction fragments are ligated together to form a pair of segments which serves as a tag for the restriction fragment (see Abstract). According to tenet (B) of MPEP 2141, the Examiner may not consider a portion of a reference, such as col. 2 of Macevicz (see Office Action, pages 10-11), without relating the disclosure to the reference as a whole. Applicants submit that an art worker seeking to identify a nucleic acid sequence would not have turned to a reference, such as Macevicz, that addresses a different problem, namely that of analyzing the frequency of sequences in a population of polynucleotides.

Furthermore, according to MPEP 2141, the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. By isolating the disclosure

of col. 2 of Macevicz, the Office Action appears to have engaged precisely in just such impermissible hindsight.

Finally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (MPEP Section 2143). The Office Action cites Macevicz on page 11, 2nd paragraph, without offering any basis for modifying Kamb and Okayama, or for combining their teachings with those of Macevicz. Therefore, the prima facie case of obviousness based on Kamb in view of Okayama, and further in view of Macevicz, fails.

In view of the foregoing comments, reconsideration and withdrawal of the rejection is requested.

CONCLUSION

Applicants submit that the application is in condition for allowance and such action is respectfully requested.

Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

The Commissioner is hereby authorized to charge payment of any additional filing fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 15966-539 CIP).

Respectfully submitted,

Dated: 16 July 2001

Ivor R. Elrifi, Reg. No. 39,529
David E. Johnson, Reg. No. 41,874
Attorneys for Applicants
c/o MINTZ, LEVIN
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241

APPENDIX

27. (Amended) A method of identifying a nucleic acid sequence, the method comprising:

(a) providing a population of nucleic acid molecules comprising at least [a first subset] one set of nucleic acid molecules[, the first subset of nucleic acid molecule further comprising at least a second subset of nucleic acid molecules];

(b) [separating] fractionating the [first subset] set of nucleic acid molecules from other nucleic acid molecules in the population[of nucleic acid molecules];

(c) isolating the [first subset] fractionated set of nucleic acid molecules;

(d) constructing a first library with the isolated [first subset] set of nucleic acid molecules, wherein [one or more members of] the first library comprises [the second] a subset of one or more member nucleic acid molecules [and wherein one or more members of the library is distinguishable from at least one of the other members of the library];

(e) recovering nucleic acids comprising the subset from [one or more members of] the first library;

(f) [separating] fractionating the [second] recovered subset [of nucleic acid molecules] from at least some of the other [members] recovered nucleic acids [in the library];

(g) isolating at least one member nucleic acid molecule from the [second] fractionated subset of nucleic acid molecules; and

(h) sequencing [the] an isolated member nucleic acid molecule, thereby identifying a nucleic acid sequence.

30. (Amended) The method of claim 29, wherein the cDNA molecules comprise a second library selected from the group consisting of a collection of sequences derived from the 5' end of RNA molecules, a [library] collection of sequences derived from the internal regions of RNA molecules, and a [library] collection of sequences derived from the 3' end of RNA molecules.

32. (Amended) The method of claim 27, wherein the population of nucleic [acids] acid molecules comprises genomic DNA.

33. (Amended) The method of claim 27, wherein the population of nucleic [acids] acid molecules comprises a normalized population of nucleic acids.

34. (Amended) The method of claim 27, wherein the [first subset] set of nucleic acid molecules [are separated] is fractionated from other nucleic [acids] acid molecules in the population of nucleic [acids] acid molecules by size.

35. (Amended) The method of claim 34, wherein said [separation] fractionation is by electrophoresis.

38. (Amended) The method of claim 27, wherein [the] members of the [first subset] set of nucleic [acids] acid molecules differ from one another by 20 or fewer nucleotides in length.

39. (Amended) The method of claim 27, wherein [the] members of the [first subset] set of nucleic [acids] acid molecules differ from one another by 15 or fewer nucleotides in length.

40. (Amended) The method of claim 27, wherein[the] members of the [first subset] set of nucleic [acids] acid molecules differ from one another by 12 or fewer nucleotides in length.

41. (Amended) The method of claim 27, wherein [the] members of the [first subset] set of nucleic [acids] acid molecules differ from one another by 8 or fewer nucleotides in length.

42. (Amended) The method of claim 27, wherein [the] members of the [first subset] set of nucleic [acids] acid molecules by 6 differ from one another or fewer nucleotides in length.

43. (Amended) The method of claim 27, wherein the population of nucleic [acids] acid molecules comprises nucleic acids having terminal sequences identical to those produced by digestion of a nucleic acid molecule with one or more restriction endonucleases.

44. (Amended) The method of claim 43, wherein the restriction endonuclease is a Type II or Type IIS restriction [endonuclase] endonuclease.

47. (Amended) The method of claim 27, wherein the first library is prepared by a process comprising:

(a) ligating the isolated [first subset] set of nucleic acid molecules to a vector to form a population of vector-insert nucleic acid molecules;

(b) transforming the vector-insert nucleic acid molecules into a host cell to form [a] the first library; and

(c) culturing the first library under conditions that allow for at least some members of the first library to be distinguished from other members of the first library.

50. (Amended) The method of claim 27, wherein two or more [members of the library] member nucleic acid molecules are [combined] pooled prior to [separating] fractionating the [second] recovered subset of nucleic acid molecules.

51. (Amended) The method of claim 27, wherein the [second] recovered subset of nucleic acid molecules [are separated] is fractionated by size.

52. (Amended) The method of claim 27, wherein the [second] recovered subset of nucleic acid molecules [are separated] is fractionated by [electropheresis] electrophoresis.

54. (Amended) The method of claim 27, wherein the isolated member nucleic acid molecule is compared to one or more known nucleic acid sequences prior to sequencing.